

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference,
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/053495

International filing date (day/month/year)
15.12.2004

Priority date (day/month/year)
16.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07J71/00, A61K9/00

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1 (a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Helps, I

Telephone No. +49 89 2399-8209



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/053495

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/053495

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 39, 40(part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 39, 40(part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/053495

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-20, 24, 32, 34, 37, 38, 40, 41
	No: Claims	21-23, 25-31, 33, 35, 36, 39
Inventive step (IS)	Yes: Claims	1-20
	No: Claims	21-41
Industrial applicability (IA)	Yes: Claims	1-38,41
	No: Claims	39,40 see below

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/053495

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43*bis*.1 and 70.9)
see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

IV. LACK OF UNITY OF INVENTION

The claims on file do not meet the requirements of unity of invention (Rule 68 PCT) for reasons given in the annex to the International Search Report. The additional fees have been paid. This Written Opinion has therefore been drawn for all claims.

V. CITATIONS AND EXPLANATIONS

The following documents are mentioned in this Written Opinion.

US-A-5,482,934	(A)
US-B1-6,392,036	(B)
WO-A-03 086437	(C)
Current Opinion in Investigational Drugs, vol. 3, p.78-83 (2002)	(D)
WO-A-2004 004739	(E)
WO-A-01 28562	(F)
WO-A-02 83113	(G)
DE-A-10 145 361	(H)
US-A-2004 023935	(I)
WO-A-2004 054545	(J)

The novel feature of the process of claim 1 is the use of an autoclave in the method of preparing the sterile aqueous ciclesonide suspension. Claims 2-20 which describe preferred embodiments of the process of claim 1 are novel by consequence. Claims 1 to 20 therefore meet the Novelty requirements of Article 33(2) PCT.

Document (F) discloses a pharmaceutical composition for nebulization containing an aqueous suspension of ciclesonide as well as a water soluble polymer, an osmotic pressure controlling agent and a surfactant (see page 5 line 14 to page 7 line 36). The water soluble polymer may be hydroxypropyl cellulose, and the osmotic pressure controlling agent may be glucose. Since glucose is a non ionic excipient, claim 21 is rendered not novel. The osmotic pressure of the compositions of document (F) can be up to 290 mOsm (see page 6, lines 10-15). Thus claims 22 and 23 are rendered not novel.

Glucose is used in (F) to control the osmolality of the composition, thus claims 25 to 27 are rendered not novel. Claim 28 is rendered not novel because the compositions of (F) contain suspending agents, preservatives and pH modifying agents (see page 6 line 24 to page 7 line 10). Claim 29 is rendered not novel because the excipients such as glucose and polysorbate are non ionic. Claim 30 is not novel because the compositions of (F) can contain citric acid (see page 7 line 8). Claim 31 is also rendered not novel because methylcellulose, hydroxypropyl cellulose, or hydroxypropyl methyl cellulose can be present in the compositions of (F) (see page 5 lines 30-37). Claim 33 is also not novel because the concentration of ciclesonide in the compositions of (F) lies within the range given in claim 33 (see page 6, lines 34-37). Claim 35 appears to be not novel because although document (F) does not mention sterility, it appears an implicit requirement of the compositions disclosed therein, since they are to be administered as a drug. Claim 36, which is a combination of ciclesonide having the concentration range given in claim 33 and having a non ionic excipient as defined in claim 21 of 22, is also not novel. Claim 39 is also not novel because the compositions of (F) are suitable for treating conditions for which a glucocorticosteroid is indicated.

Claims 21-23, 25-31, 33, 35, 36, and 39 therefore do not meet the Novelty requirements of Article 33(2) PCT.

Claim 24 is rendered novel by the mean particle size of the ciclesonide. Claim 32 is rendered novel by the choice of suspending agent. Claim 34 is rendered novel by the mean particle size of ciclesonide. Claim 37 is rendered novel by the presence of glycerol or mannitol as well as polysorbate as excipients. Claim 38 is novel by consequence. Claim 40 is rendered novel by the choice of subject to be treated, as well as the choice of disorder and treatment regimen. Claim 41 is rendered novel by the treatment regimen to be used.

Claims 24, 32, 34, 37, 38, 40 and 41 therefore meet the Novelty requirements of article 33(2) PCT.

Document (B) discloses a method for the sterilisation of glucocorticosteroids, including ciclesonide (see column 3, line 13). In this method the micronised glucocorticosteroid powder is subjected to dry heat. Document (C) describes the sterilisation of corticosteroids

including ciclesonide using gamma ray irradiation. It would not have been obvious for the skilled man to carry out the presently claimed moist heat sterilisation, especially in view of the statement on column 2, lines 23-32 of (B).

Documents (A) and (D) give general background on the preparation and use of ciclesonide, but do not mention sterilisation.

Inventive step (Article 33(3) PCT) can be recognised for claims 1-20 because the problem of providing an alternative method of sterilising ciclesonide suspensions for nebulisation has been solved in a non obvious manner.

Document (G) discloses sterile compositions for nebulization which contain a steroidal anti-inflammatory agent, including ciclesonide (see claim 30). The compositions are sterile (see page 17, line 7), and the steroid may be in aqueous suspension, (page 19, lines 13-19). Non-ionic excipients may also be present, including emulsifying agents such as polysorbates (see page 26 lines 6-24). Propylene glycol or glycerol may be present in the composition (see page 19, lines 12-19), and agents for controlling the pH, as well as complexing agents and preservatives may be present (see page 24, line 15-page 25, line 10). Citric acid is used as pH controlling agent (see page 24, line 11). Polysorbates including polyoxyethylene sorbitan fatty acid esters, as well as hydroxypropyl cellulose or hydroxypropyl methyl cellulose are used as emulsifiers (see page 26, line 8 to page 27, line 10).

Document (H) discloses sterile compositions for nebulization which contain a steroid, for example ciclesonide (see claim 3) which is an aqueous suspension with a particle size of 0.5-2.0 micrometers (see claim 10). The compositions also contain polysorbate 80 as a non-ionic excipient (see page 6, paragraph 26).

Although documents (G) and (H) do not disclose any novelty destroying examples, it is noted that the particle size for ciclesonide specified in claims 24 and 34 appears to be in the usual range for ciclesonide suspensions for nebulization (see above). Thus claims 24 and 34 cannot be considered to be inventive. The choice of suspending agents in claim 32 cannot be considered inventive because these appear to be known from (G) and (H) as suspending agents. Also, polysorbate and glycerol are known excipients for aqueous

suspensions for nebulization (see above), and the presence of both in the ciclesonide composition cannot be considered inventive unless an unexpected effect can be shown. Also, citric acid is a known additive for control of pH. Claims 37 and 38 cannot be considered inventive. Claims 40 and 41 cannot be considered inventive because asthma is a known bronchoconstrictive agent which can be treated by ciclesonide (see Document (G) page 34), and a continuous treatment regimen is a known alternative drug delivery method.

Claims 21 to 41 therefore do not meet the inventive step requirements of Article 33(3) PCT because these claims do not describe novel subject matter or are obvious alternatives to the prior art as described above.

In the further examination procedure the Applicant is requested to file a new set of claims 21-41 in which a common novel feature is clearly defined, and to submit further information and argumentation in order to make credible the involvement of inventive step for the novel subject matter to be defined.

For the assessment of the present claims 38-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. CERTAIN CITED DOCUMENTS.

At present no priority document is available. The examination has been carried out assuming that the priority date is validly claimed. If during the subsequent procedure (e.g. EPO examination) the priority date is found to be invalid for some or all of the presently claimed subject matter, the intermediate documents (E), (I) and (J) may be taken into consideration for the evaluation of Novelty and/or inventive step.

VII. CERTAIN DEFECTS IN THE INTERNATIONAL APPLICATION.

In order to meet the requirements of Rule 5.1(a)(ii) PCT, documents (A)-(D) and (G)-(H) should be identified in the description and the relevant prior art disclosed therein should be briefly discussed.

VIII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION.

The definition of the patient as a "child" in claim 40 is not clear (Article 6 PCT) as no maximum age is given in the claim.